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EXAMINER	
BLANCHARD, DAVID J	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/669,187	KRIEG ET AL.	
	Examiner	Art Unit	
	David J Blanchard	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *4/15/2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-77,85-94 and 98* is/are pending in the application.

4a) Of the above claim(s) *40-44 and 62-73* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-39,45-61, 74-77, 85-94 and 98* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) DB
Paper No(s)/Mail Date *6/1/01; 6/14/01*.4/7/03; 2/4/04; 4/5/04; 5/24/04

4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application (PTO-152)

6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Claims 1-77, 85-94 and 98 are pending.

2 Applicant's election with traverse of Group I, claims 1-36, 77, 85-94 and 98 in the reply filed on 4/15/2004 is acknowledged. The traversal is on the grounds that a search and examination of claim 1 and claims dependent thereon would not be unduly burdensome. The response states that the nucleic acids in the instant application do not encode proteins, the nucleic acids are usable together for the purpose of immunostimulation. The response further states that the nucleic acids of the instant invention can induce an immune response useful in the treatment of one or more cancer type. These arguments are found persuasive because the nucleic acids of the instant invention are immunostimulatory nucleic acids and are to be used as an adjuvant, wherein the only active method step is administration of the immunostimulatory nucleic acid. Therefore, the restriction requirement between the Inventions of Groups I, III, XV, XVII, XIX, XXI, XXIII, XXV, XXVII, XXIX, XXXI, XXXIII, XXXV, XXXVII, and XXXIX is hereby **VACATED**. The restriction requirement between these Groups has been vacated because these Groups are drawn to a method of stimulating an immune response comprising a Py-rich nucleic acid, wherein the active method step is administration of said nucleic acid.

3. Claims 40-44 and 62-73 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention.

4. Claims 1-39, 45-61, 74-77, 85-94 and 98 are under examination. The claims are being examined to the extent that the immunostimulatory nucleic acid is a Py-rich nucleic acid.

Specification

5. The disclosure is objected to because of the following informalities:

The specification contains USSNs of Applications that have now issued as U.S. Patents at pages 25, 37 and 115. Applicant is required to update the USSNs numbers at pages 25, 37 and 115 with the corresponding U.S. Patent number. Applicant is reminded to check the entire disclosure and update any USSN of an Application that has now issued as a U.S. Patent.

Appropriate correction is required.

Claim Objections

6. Claims 1, 59 and 76-77 are objected to because of the following informalities:

a. Claim 1 and 76-77 are broadly drawn to non-elected inventions (i.e., TG-rich nucleic acids).

b. Claim 59 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim, or amend the claim to place the claim in proper dependent

form, or rewrite the claim in independent form. Claim 56 from which claim 59 depends recites "wherein the subject is a human" and claim 59 does not further limit the human subject. Instead claim 59 recites that the subject is selected from a dog, cat, horse, cow, pig, sheep, goat, chicken, monkey and a fish, which is a broader scope than base claim 56.

c. Claims 86, 88 and 89 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claims, or amend the claims to place the claims in proper dependent form, or rewrite the claims in independent form. Claims 86, 88 and 89 recite that the poly T motifs comprise "at least three contiguous T nucleotide residues". Claims 86, 88 and 89 depend from base claim 5, which depends from base claim 3, which recites that the poly T nucleic acid comprises four contiguous T nucleotide residues (i.e., 5' TTTT 3'), meaning that any claim that depends from this base claim must also comprise at least four contiguous T nucleotide residues as well as additional elements, which would further limit the base claim. Thus, claims 86, 88 and 89 do not further limit base claims 5 and 3, from which they depend.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 11-15, 61, 85 and 98 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 61 recites the limitation "the antigen". There is insufficient antecedent basis for this limitation in the claim. Claim 59 from which claim 61 depends does not recite "antigen".

b. Claim 98 recites the limitation "the plurality of CpG motifs". There is insufficient antecedent basis for this limitation in the claim. Claim 90 from which claim 98 depends does not recite any CpG motif.

c. Claims 11-15 recite the limitation "the T-rich immunostimulatory nucleic acid". There is insufficient antecedent basis for this limitation in the claim. Claim 1 from which claims 11-15 depend recites a Py-rich nucleic acid and not a T-rich nucleic acid.

d. Claim 85 is indefinite for reciting "T motifs". It is unclear if the claim is drawn to nucleic acids comprising a single T nucleic acid or a plurality of single T nucleic acids (e.g., CAGTGG and CAGTGGTCGTC) or did Applicant intend to recite "poly T motifs"?

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-16, 18-24, 26-39, 45-61, 74-77, 85-94, and 98 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of stimulating an immune response comprising administering a Py-rich or T-rich immunostimulatory nucleic acid and a method of stimulating an immune response and an innate immune response in a non-rodent subject comprising administering a CpG containing Py-rich or T-rich immunostimulatory nucleic acid, does not reasonably provide enablement for (i) a method of stimulating an immune response and an innate immune response in a non-rodent subject comprising administering a non-CpG Py-rich or non-CpG T-rich immunostimulatory nucleic acid or (ii) a method of stimulating an immune response comprising administering a polycytosine homopolymer or a polythymidine homopolymer shorter than 21 nucleotides or (iii) a method for treating or preventing asthma, allergy, infectious disease and cancer comprising stimulating an immune response in a non-rodent subject comprising administering a CpG or non CpG Py-rich or T-rich immunostimulatory nucleic acid, wherein the cancer treatment further comprises administering an anti-cancer therapy selected from the group consisting of a chemotherapeutic agent, an immunotherapeutic agent and a cancer vaccine. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in

the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are drawn to a method of stimulating an immune response in a non-rodent subject comprising administering a Py-rich or T-rich immunostimulatory nucleic acid for treating or preventing asthma, allergy, infectious disease and treating or preventing cancer wherein the cancer treatment further comprises an anti-cancer therapy selected from the group consisting of a chemotherapeutic agent, an immunotherapeutic agent and a cancer vaccine.

The specification teaches that synthetic oligodeoxynucleotides (ODN) that are T-rich nucleic acids without a CpG motif, can induce stimulation of human B cells *in vitro* (see Example 6, page 134) and the length of the sequence of synthetic poly T ODNs has an important impact on its *in vitro* activity (see Figure 5 and page 134). Example 7 teaches that synthetic non-CpG containing poly T ODNs also enhance NK activiation, NK cytotoxicity and monocyte activation *in vitro* (see pages 135-137). The specification also teaches that synthetic T-rich ODNs with and without a CpG dinucleotide can induce the secretion of the pro-inflammatory cytokines TNFalpha and IL-6 *in vitro* (see Figures 11 and 12 and Example 8 at page 137). The specification states "Since we saw not only quantitative, but also qualitative differences in activities of different CpG ODNs in mice, we first screened a panel of CpG and non-CpG control ODN on mouse cells to find *in vitro* assays with reliable and strong correlation to *in vivo* adjuvant activity with

hepatitis B surface antigen (HbsAg)." (see page 148). Example 12 and the continuing text of the specification is directed towards testing CpG containing ODNs in chimpanzees and monkeys and not Py-rich or T-rich ODNs lacking CpG motifs. The specification teaches that the sequence, number and spacing of individual CpG motifs contribute to the immunostimulatory activity of a CpG phosphorothioate ODN (see page 148). At page 152, the specification teaches that the immunostimulatory activity of ODNs without CpG motifs was negative or weak compared to CpG ODNs and ODNs with non-optimal CpG motifs were less active than ODNs containing CpG motifs flanked by two 5' purines and two 3' pyrimidines (see page 152, lines 10-17). The specification does not teach any *in vivo* activity or *in vivo* immune stimulation associated with the administration of the Py-rich or T-rich ODNs lacking a CpG dinucleotide to non-rodent subject (e.g., human subject). The specification does not predict or teach any positive therapeutic benefit (i.e., treating or preventing) correlated with the administration of a non-CpG or CpG containing Py-rich or T-rich ODN in a non-rodent subject. Further, the specification does not teach any positive therapeutic outcome associated with stimulating an immune response in a non-rodent subject comprising administering a Py-rich or T-rich (with or without CpG dinucleotide) immunostimulatory nucleic acid, wherein asthma, allergy, infectious disease and cancer were treated or prevented in a non-rodent subject commensurate in scope with the claims.

With respect to treating and preventing cancer, it is well known in the art that tumor cells in vivo simply do not display their unique antigens in ways that are easily recognized by cytotoxic T lymphocytes (Ezzell; page 48, column 2, paragraph 2). Forni

et al (Cancer Research, 2000, 60; 2571-2575) disclose tumor cells have the ability to escape immune reactions and tumor masses can suppress immune attack (see page 2571, right column). Mouse models show that elicitation of a significant immune response in patients with advanced tumors is exceedingly difficult, and only a minority of tumor-bearing mice are cured. "As a tumor increases in size, it becomes refractory to immunotherapy" (see page 2571, left column). A similar picture is emerging from Phase I immunotherapy trails where only a few patients with established tumors display objective and in any event temporary responses (see page 2571, right column). Tumor burden and antigenic drift continue to present serious burdens for successful cancer therapy *in vivo*. Tumors are classified as immunogenic or non-immunogenic, solid or hematological in nature. Effective cancer strategies should be designed to deal effectively with the nature of each of these classifications.

Donnelly J. (Nature Medicine, 11(9): 1354-1356, Nov. 2003) states "treating cancer with something that looks more like a modern-day vaccine, with a defined antigen and an optimized adjuvant and delivery platform, is still in the future" (see page 1354 lines 13-17). Further, DeGruijl T. D. et al (Nature Medicine, 5(10):1124-1125, Oct. 1999) state that a variety of anti-tumor vaccine trials have been undertaken and in spite of the large number of these trials, and the plethora of distinct approaches investigated, there has been little evidence of clinical efficacy. DeGruijl also states "precise correlates of clinical effects and immunological responses have been lacking" (see page 1124, left column).

It has been an art-recognized experience that for any novel therapy, the transition from the laboratory to the clinic (animal experiments to bedside) is a quantum leap (Chatterjee et al., Cancer Immunology and Immunotherapy, 38:75-82, 1994). Results obtained under controlled conditions and in inbred animals often differ from the clinical response obtained in patients. This applies in particular to strategies based on immune responses.

Vollmer et al (Antisense and Nucleic Acid Drug Development, 12:165-175, 2002) teach specific sequence requirements of CpG-free phosporothioate oligodeoxynucleotides (ODNs) for *in vitro* immunostimulatory activity, specifically the thymidine content and the length of a phosporothioate-ODNs determine the immunostimulatory potential (see entire document). Vollmer et al teach that a polycytosine ODN (i.e., Py-rich), such as ODN 2178 (see Table 1) is essentially immunologiocally inert (see page 168, right column) and a short polythymidine ODN with 18 nucleotides showed background activity, whereas increasing the length resulted in a progressively strong increase in stimulation for polythymidine ODNs 2195 (21 bases), 2183 (24 bases), and 2194 (27 bases) (see page 169, left column and Figure 2). According to Vollmer et al, short non-CpG phosphorothioate ODN induces only minimal stimulation *in vivo* as well as *in vitro* and that ODNs equal or greater than 24 nucleotides are needed to induce stronger stimulation (see page 173, right column) and Vollmer et al states "Nevertheless, *in vitro* longer non-CpG T-rich ODNs are always less efficient and potent than CpG ODNs, and, therefore, they might induce weaker *in vivo* effects that are not sufficient to mediate efficiently a Th1-dominated immune response."

The skilled artisan would not predict or anticipate that such a weak immunostimulatory response illicited by non-CpG T-rich ODNs as an effective treatment or preventative therapy for asthma, allergy, infectious disease and cancer. Vollmer et al teaches that the mechanism of immune activation by non-CpG ODNs remains to be elucidated. In agreement with the teachings of Vollmer, McCluskie et al (Vaccine, 19:2657-2660, 2001) teaches a polythymidine nucleic acid twenty nucleotides in length (ODN 1983), which did not have an immunostimulatory effect in immunized mice (see page 2658 and Figures 1-2). Further, Jones et al (Vaccine, 17:3065-3071, 19999) teach a T-rich immunostimulatory nucleic acid lacking CpG dinucleotides as a negative control for testing ODNs *in vivo* for their adjuvant activities in monkeys (see page 3066, right column and page 3067 and Figures 1-2).

In vitro animal model studies have not correlated well with *in vivo* clinical trial results in patients. Since the therapeutic indices of immunotherapeutic regimens can be species- and model-dependent, it is not clear that reliance in the *in vitro* stimulation of immune cells with Py-rich and T-rich ODNs and the *in vivo* mouse and non-human primate experimental models with CpG containing ODNs accurately reflects the relative efficacy of the claimed therapeutic strategy based upon *in vitro* stimulation of B cells, Nk cell and monocytes.

There is insufficient evidence or nexus that would lead the skilled artisan to predict the ability to treat or prevent asthma, allergy, infectious disease, and cancer in a non-rodent subject comprising administering a Py-rich or T-rich (with or without a CpG dinucleotide) immunostimulatory ODN. The specification provides insufficient guidance

and direction to the skilled artisan as how to extrapolate *in vitro* immune stimulating data obtained with B cells, Nk cells and monocytes and data obtained from non-human primate models using only immunostimulatory sequences comprising CpG dinucleotides to the development of a non-CpG Py-rich or non-CpG T-rich immunostimulatory ODN correlated with a positive therapeutic outcome (i.e., treating or preventing) in a non-rodent subject, particularly in view of the teachings of Vollmer et al, McCluskie et al and Jones et al.

In view of the lack of the predictability of the art to which the invention pertains the lack of established clinical protocols for effective adjuvant therapies, undue experimentation would be required to practice the claimed Py-rich or T-rich ODNs with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed Py-rich or T-rich ODNs and absent working examples providing evidence which is reasonably predictive that the claimed Py-rich or T-rich ODNs are effective for treating and preventing asthma, allergy, infectious disease, and cancer, commensurate in scope with the claimed invention.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

11. Claims 1-13, 16-19, 21-22, 24-25, 37, 39, 77, 85-87, 90-92, 94 and 98 are rejected under 35 U.S.C. 102(a) as being unpatentable over Jones et al (Vaccine, 17:3065-3071, August 6, 1999).

The claims are interpreted as drawn to a method of stimulating an immune response in a non-rodent subject comprising administering a Py-rich nucleic acid which is a T-rich nucleic acid having the formula 5'-X_1X_2TTTTX_3X_4-3', wherein X_1, X_2, X_3 and X_4 are nucleotides. The T-rich nucleic acid comprises a plurality of interspersed poly T motifs, wherein at least one of the poly T motifs comprises at least 5, 6, 7, or at least 8 contiguous nucleotide residues and X_1X_2 is TT and X_3X_4 is TT or dinucleotides recited in claims 8 and 9. The T-rich nucleic acid comprises greater than 25%, 35%, 40%, 50% and 60%T and the Py-rich nucleic acid is at least 20 and 24 nucleotides long and has a nucleotide backbone modification, which is a phosphorothioate modification. The Py-rich nucleic acid is free of CpG dinucleotides, and is free of methylated CpG dinucleotides and is free of two and free of three CpG dinucleotides (claims 91-92) and is free of two poly A sequences of at least 3 contiguous A nucleotide residues (claim 94) and free of poly-C sequences. The method of inducing an immune response in a non-rodent subject with a Py-rich nucleic acid also encompasses exposing the subject to an

antigen, wherein the antigen is a peptide antigen and induces an antigen-specific immune response and wherein the subject has or is at risk of developing an infectious disease, wherein the method is for treating an infectious disease. Claim 77 is drawn to a method of inducing an innate immune response comprising administering a T-rich immunostimulatory nucleic acid. Claims 85-87 are interpreted as drawn an immunostimulatory nucleic acid comprising at least 3, at least 4, at least 5, at least 6, at least 7, or at least 8 T motifs and at least two of the poly T motifs comprise at least three contiguous T nucleotide residues and at least four contiguous T nucleotide residues.

Jones et al teach a method of stimulating an immune response in monkeys (non-rodent subject) comprising administering synthetic oligodeoxynucleotides (ODN) and a synthetic peptide (PADRE 45) derived from the circumsporozoite protein from *Plasmodium falciparum* (see abstract). The ODNs administered included one CpG containing Py-rich or T rich ODN as follows: 5' TCGTCGTTTTGTCGTTTTGTCGTT 3' (ODN 2006) (see page 3066, right column). A second ODN administered is 5' CTGGTCTTTCTGGTTTTTTTCTGG 3' (ODN 2041) (see page 3066, right column). Thus, Jones et al teach a method of stimulating an immune response in a non-rodent subject comprising a Py-rich nucleic acid which is a T-rich nucleic acid 24 nucleotides in length having the formula 5'-X_1X_2TTTTX_3X_4-3', wherein X_1, X_2, X_3 and X_4 are nucleotides. The T-rich nucleic acid comprises a plurality of interspersed poly T motifs, wherein at least one of the poly T motifs comprises at least 5, 6, or at least 7 contiguous nucleotide residues and X_1X_2 is TT and X_3X_4 is TT or dinucleotides GT and GG as recited in claim 8 and dinucleotides TC and CT as recited in claim 9. The synthetic

ODNs taught by Jones et al are T-rich nucleic acids comprising 58% T, which is greater than 25%, 35%, 40%, 50% T and the Py-rich nucleic acid has a nucleotide backbone modification, which is a nuclease resistant phosphorothioate backbone, which is interpreted as "entirely modified". Additionally, ODN 2041 is a Py-rich or T-rich nucleic acid that is free of CpG dinucleotides, and is free of methylated CpG dinucleotides and is free of two and free of three CpG dinucleotides (claims 91-92) and both ODNs 2006 and 2041 are free of two poly A sequences of at least 3 contiguous A nucleotide residues and free of poly-C sequences. Further, the ODNs taught by Jones et al are T-rich immunostimulatory nucleic acids comprising at least 3 T motifs and at least two of the poly T motifs comprise at least three contiguous T nucleotide residues and at least four contiguous T nucleotide residues. Because Jones et al teach a method of inducing an immune response in a non-rodent subject and because innate immunity operates nonspecifically during the early phases of an immune response, it is the Examiner's position that Jones et al teach a method of stimulating or inducing an innate immune response, wherein the active method step comprises administering a T-rich immunostimulatory nucleic acid. Thus, Jones et al anticipates the claims.

12. Claims 1-13, 16-19, 21, 24-25, 30, 33-34, 36-39, 77, 85-87, 94 and 98 are rejected under 35 U.S.C. 102(e) as being anticipated by Krieg et al (U.S. Patent 6,239,116 B1, 10/30/1997, Ids reference A38).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art

under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

The claims and their interpretation have been described supra.

Claim 30 recites wherein the immunostimulatory nucleic acid is administered orally; claim 38 recites wherein a nucleic acid encodes the antigen administered to the subject, which is separate from the immunostimulatory nucleic acid. Claim 33 recites wherein the immunostimulatory nucleic acid is administered mucosally to a mucosal surface and the immune response is a mucosal immune response (claim 34); claim 36 recites wherein the mucosal surface is selected from the group consisting of an oral, nasal, rectal, vaginal, and ocular surface.

Krieg et al teaches a method of stimulating an immune response in a human, a dog, cat, horse, cow, pig, sheep, goat, chicken, monkey, rat, and mouse comprising administering Py-rich or T rich immunostimulatory nucleic acid (see Tables 11-13, SEQ ID NOS:78, 53, 80, 82, 56, 49, 78, 53, 86, 46 and 48 and columns 6-7), wherein the immunostimulatory nucleic acid is unmethylated (i.e., free of methylated CpG) and has a backbone modification comprising a phosphorothioate modification and is interpreted as being "entirely modified" (see column 14, lines 3-9). Thus, Krieg et al teach a method of stimulating an immune response in a non-rodent subject comprising a Py-rich nucleic acid which is a T-rich nucleic acid 24 nucleotides in length (see SEQ ID NO:46, Table 12) having the formula 5'-$X_1X_2TTTTX_3X_4$-3', wherein X_1, X_2, X_3 and X_4 are

nucleotides. The T-rich nucleic acid comprises a plurality of interspersed poly T motifs and X_1X_2 is TT and X_3X_4 is TT or dinucleotide GT as recited in claim 8 and dinucleotides TG and GT as recited in claim 9 (see SEQ ID NO:53, Table 11). The immunostimulatory nucleic acids taught by Krieg et al are T-rich nucleic acids comprising greater than 50% T and the immunostimulatory nucleic acids are free of two poly A sequences of at least 3 contiguous A nucleotide residues and free of poly-C sequences (see Tables 11-13, SEQ ID NOS:78, 53, 80, 82, 56, 49, 78, 53, 86, 46 and 48). Further, the immunostimulatory nucleic acids taught by Krieg et al are T-rich immunostimulatory nucleic acids comprising at least 3 T motifs (interpreted as single T motifs, see 112, 2nd above) and at least two of the poly T motifs comprise at least three contiguous T nucleotide residues and at least four contiguous T nucleotide residues (see Table 12, SEQ ID NO:46). Krieg et al teach that the immunostimulatory nucleic acid is administered orally (see column 46, lines 55-64) and oral administration is also interpreted as a mucosal administration, which would inherently induce a mucosal immune response. Krieg et al teach that the immunostimulatory nucleic acid can be administered in conjunction with an antigen or a DNA vaccine encoding an antigen, wherein the DNA is separate from the immunostimulatory nucleic acid and the antigen determines the specificity of the immune response (i.e., is an antigen-specific immune response) (see column 45, lines 36-49). Because Krieg et al teach a method of inducing an immune response in a non-rodent subject and because innate immunity operates nonspecifically during the early phases of an immune response, it is the Examiner's position that Krieg et al teach a method of stimulating or inducing an innate

immune response, wherein the active method step comprises administering a T-rich immunostimulatory nucleic acid. Thus, Krieg et al anticipates the claims.

13. Claims 1-13, 16-21, 23-25, 30-31, 33-34, 36-39, 77, 85-87, 92, 94 and 98 are rejected under 35 U.S.C. 102(b) as being unpatentable over Davis et al (WO 98/40100, 9/17/1998, Ids reference B1).

The claims and their interpretation have been described supra.

Claim 20 recites wherein the immunostimuklatory nucleic acid has a chimeric nucleotide backbone; claim 23 recites wherein the immunostimulatory nucleic acid is free of unmethylated CpG dinucleotides; claim 31 recites wherein the immunostimulatory nucleic acid is administered locally.

Davis et al teach a method of stimulating an immune response in any mammalian subject, preferably a human (see page 15, line 21) comprising administering Py-rich or T rich immunostimulatory nucleic acid (see page 12, SEQ ID NOS:6, 8, 10 and 14), wherein the immunostimulatory nucleic acid is methylated or unmethylated (i.e., free of methylated CpG) and has a backbone modification comprising a phosphorothioate modification rather than phosphodiester linkages (i.e, interpreted as entirely modified) or comprises a modification at the 5' end (i.e., backbone is chimeric) (see page 7, lines 21-28). Thus, Davis et al teach a method of stimulating an immune response in a non-rodent subject comprising a Py-rich nucleic acid which is a T-rich nucleic acid at least 24 nucleotides in length (see SEQ ID NO:6, page 12) having the formula 5'-$X_1X_2TTTTX_3X_4$-3', wherein X_1, X_2, X_3 and X_4 are

nucleotides. The T-rich nucleic acid comprises a plurality of interspersed poly T motifs and X_1X_2 is TT and X_3X_4 is TT or dinucleotide GT as recited in claim 8 and dinucleotides TG and GT as recited in claim 9 (see SEQ ID NO:14, page 12). The immunostimulatory nucleic acids taught by Davis et al are T-rich nucleic acids comprising greater than 50% T and the immunostimulatory nucleic acids are free of two poly A sequences of at least 3 contiguous A nucleotide residues and free of poly-C sequences (see page 12). Further, the immunostimulatory nucleic acids taught by Davis et al are T-rich immunostimulatory nucleic acids comprising at least 3 T motifs (interpreted as single T motifs, see 112, 2nd above) and at least two of the poly T motifs comprise at least three contiguous T nucleotide residues and at least four contiguous T nucleotide residues and is free of three CpG dinculeotides (see page 12, SEQ ID NO:6). Davis et al teach that the immunostimulatory nucleic acid is administered orally (see page 17, line 21) and locally (see page 18, line 11) and oral administration is also interpreted as a mucosal administration, which would inherently induce a mucosal immune response. Davis et al teach that the immunostimulatory nucleic acid can be administered in conjunction with an antigen or a DNA vaccine encoding an antigen, wherein the DNA is separate from the immunostimulatory nucleic acid and the antigen determines the specificity of the immune response (i.e., is an antigen-specific immune response) (see page 3, lines 24-27, pages 13-15 and pages 27-28). Because Davis et al teach a method of inducing an immune response in a non-rodent subject and because innate immunity operates nonspecifically during the early phases of an immune response, it is the Examiner's position that Davis et al teach a method of stimulating or inducing an innate immune

response, wherein the active method step comprises administering a T-rich immunostimulatory nucleic acid. Thus, Davis et al anticipates the claims.

Double Patenting

14. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

15. Claims 1-5, 10-13, 16, 18-21, 25, 30-33, 36-39, 45-49, 52-61, 77, 85-87, 90, 94 and 98 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 46-58, 64-66, 71-74, 77-78, 80-81, 84, 89-90, 95-96 and 98 of copending USSNs 10/613,228; 10/613,739; 10/613,736 in view of Krieg et al (U.S. Patent 6,239,116 B1, 10/30/1997, Ids reference A38). Although the conflicting claims are not identical, they are not patentably distinct from each other.

The claims in the instant application are drawn to a method of stimulating an immune response in a non-rodent subject for treating or preventing asthma, allergy, infectious disease and cancer comprising administering a Py-rich nucleic acid, which is

a T-rich nucleic acid having the formula 5'-$X_1X_2TTTTX_3X_4$-3', wherein X_1, X_2, X_3 and X_4 are nucleotides and the T-rich nucleic acid may comprise a plurality of interspersed poly T motifs comprising at least 5 contiguous nucleotide residues (i.e., T residues) and comprises greater than 25%, 35%, 40% and 50% T. The Py-rich immunostimulatory nucleic acid comprises at least 20 nucleotides, is free of two poly A sequences of at least 3 contiguous A residues and has a nucleotide backbone modification, which is a phosphorothioate modification, a chimeric nucleotide backbone, or the nucleotide backbone is entirely modified and the immunostimulatory nucleic acid is free of poly-C sequences. The immunostimulatory nucleic acid comprises at least 3, at least 4, at least 5, at least 6, at least 7, or at least 8 T motifs and at least two of the poly T motifs comprise at least three contiguous T nucleotide residues or at least four contiguous T nucleotide residues. The immunostimulatory nucleic acid is administered orally, locally, in a sustained release device, mucosally to a mucosal surface, wherein the mucosal surface is selected from the group consisting of an oral, nasal, rectal, vaginal, and ocular surface. The method of inducing an immune response in a non-rodent subject with a Py-rich nucleic acid further comprises administering an antigen encoded by a nucleic acid vector administered to the subject separately from the immunostimulatory nucleic acid or the antigen is a peptide antigen. The method for treating cancer comprises administering a Py-rich immunostimulatory nucleic acid to a subject, wherein the subject is a human or is selected from, a dog, a cat, and a horse. The method of stimulating an immune response in a human comprising administering a Py-rich nucleic acid, further comprises administering an antibody specific for a cell surface antigen and

an antigen selected from a bacterial antigen, a viral antigen, a parasitic antigen, a fungal antigen and an antigen derived from a microorganism (claim 61), wherein the subject is a human or is selected from a dog, cat, horse, cow, pig, sheep, goat, chicken, monkey and fish. Claim 77 is drawn to a method of inducing an innate immune response comprising administering a T-rich immunostimulatory nucleic acid.

Claims 46-58, 64-66, 71-74, 77-78, 80-81, 84, 89-90, 95-96 and 98 in copending USSNs 10/613,228; 10/613,739; 10/613,736 are drawn to a method for stimulating an immune response in a subject that has or is at risk of developing a bacterial infection, a viral infection, a fungal infection, a parasite infection, allergy, asthma, or cancer (compare claim 95 with claim 48 of the instant application) comprising administering an immunostimulatory nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:1, which has the sequence 5' tcgtcgtttttcgtgcgttttt 3'. Thus, SEQ ID NO:1 is a Py-rich or T-rich nucleic acid having the formula 5'-$X_1X_2TTTTX_3X_4$-3', wherein X_1, X_2, X_3 and X_4 are nucleotides and comprises a plurality of interspersed poly T motifs comprising at least 5 contiguous nucleotide residues (i.e., T residues) and comprises greater than 25%, 35%, 40% and 50% T. The immunostimulatory nucleic acid of SEQ ID NO:1 comprises at least 20 nucleotides, is free of two poly A sequences of at least 3 contiguous A residues and has a nucleotide backbone modification, which is a phosphorothioate modification, a chimeric nucleotide backbone, or the nucleotide backbone is entirely modified and the immunostimulatory nucleic acid is free of poly-C sequences. The immunostimulatory nucleic acid comprises at least 3, at least 4, at least 5, at least 6, at least 7, or at least 8 T motifs (interpreted as a single T motif, see

112, 2nd above) and at least two of the poly T motifs comprise at least three contiguous T nucleotide residues or at least four contiguous T nucleotide residues. The immunostimulatory nucleic acid is administered orally, locally, in a sustained release device, mucosally to a mucosal surface, wherein the mucosal surface is selected from the group consisting of an oral, nasal, rectal, vaginal, and ocular surface. The method of inducing an immune response in a subject with the immunostimulatory nucleic acid of SEQ ID NO:1 further comprises administering an antigen, wherein the antigen is selected from a bacterial antigen, a viral antigen, a fungal antigen, a parasitic antigen, a cancer antigen, a self antigen, and an allergen (also compare claim 61 of the instant application to claim 57 of copending USSNs 10/613,228; 10/613,739; 10/613,736). The method of stimulating an immune response in a human comprising administering the immunostimulatory nucleic acid of SEQ ID NO:1, further comprises administering an antibody specific for a cell surface antigen, wherein the subject is a human or is selected from a dog, cat, horse, cow, pig, sheep, goat, chicken, monkey, and fish. Claim 98 is drawn to a method of inducing an innate immune response comprising administering the immunostimulatory nucleic acid of SEQ ID NO:1 (compare with claim 77 of the instant application). The immunostimulatory nucleic acid species of SEQ ID NO:1 recited in claims 46 and 98 in copending USSNs 10/613,228; 10/613,739; 10/613,736 anticipate the genus (i.e., Py-rich or T-rich nucleic acid) recited in claims 1-4 in the instant application. The claims in copending USSNs 10/613,228; 10/613,739; 10/613,736 do not specifically teach co-administration of an immunostimulatory nucleic acid with an antigen encoded by a nucleic acid vector, wherein the immunostimualtory

nucleic acid is separate from the nucleic acid vector encoding the antigen. This deficiency is made up for in the teachings of Krieg et al.

Krieg et al teach a method of inducing an immune response in a subject comprising administering a Py-rich or T-rich immunostimulatory nucleic acid and a DNA vaccine encoding an antigen, wherein the DNA vaccine is separate from the immunostimulatory nucleic acid.

The claims in the instant application are obvious variants of copending USSNs 10/613,228; 10/613,739; 10/613,736 because it would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a method of inducing an immune response in a non-rodent subject comprising administering a Py-rich or T-rich immunostimulatory nucleic acid and an antigen encoded by a nucleic acid vector, wherein the immunostimulatory nucleic acid is separate from the nucleic acid vector encoding the antigen as taught by Krieg et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a method of inducing an immune response in a non-rodent subject comprising administering a Py-rich or T-rich immunostimulatory nucleic acid and an antigen encoded by a nucleic acid vector, wherein the immunostimulatory nucleic acid is separate from the nucleic acid vector encoding the antigen as taught by Krieg et al because Krieg et al teach a method of inducing an immune response in a subject comprising administering a Py-rich or T-rich immunostimulatory nucleic acid and a DNA vaccine encoding an antigen, wherein the DNA vaccine is separate from the immunostimulatory nucleic acid.

Claims 1-5, 10-13, 16, 18-21, 25, 30-33, 36-39, 45-49, 52-61, 77, 85-87, 90, 94 and 98 are directed to an invention not patentably distinct from claims 46-58, 64-66, 71-74, 77-78, 80-81, 84, 89-90, 95-96 and 98 of copending USSNs 10/613,228; 10/613,739 10/613,736. Specifically, see above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned USSNs. 10/613,228; 10/613,739 10/613,736 discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 35 U.S.C. 103(c) and 37 CFR 1.78(c) to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

16. Claims 1-13, 16-20, 24-25, 30, 34-35, 37-39, 54, 56, 77, 85-87, 94 and 98 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 5, 7-9, 16-18, 20-21, 23-25, 27-30, 34 and 40-41 of copending Application No. 10/272,502 in view of Krieg et al (U.S. Patent 6,239,116 B1, 10/30/1997). Although the conflicting claims are not identical, they are not patentably distinct from each other

The claims and their interpretation have been described supra. For this rejection the term "comprising" in the instant claims in interpreted as open language, meaning that the instant method of stimulating an immune response includes a Py-rich or T-rich nucleic acid as well as additional agents such as an imidazoquinoline agent and a C8-substituted guanosine.

Claims 5 and 7-9 in copending Application No. 10/272,502 are drawn to a method of stimulating antibody dependent cellular cytotoxicity in a subject comprising administering an antibody and an agent selected from an imidazoquinoline agent and a C8-substituted guanosine to a subject in need thereof and further comprising an immunostimulatory (ISS) nucleic acid, wherein the ISS can be a poly-T nucleic acid, or a T-rich nucleic acid and the ISS has a phosphorothioate backbone modification and the ISS has a chimeric backbone. Claims 16-18, 20-21, 23-25, 27-30, 34 and 40-41 are drawn to a method for modulating an immune response in a subject, comprising administering an ISS poly-T or a T-rich nucleic acid and an agent selected from an imidazoquinoline agent (S-28463) and a C8-substituted guanosine, wherein the immune response is antibody dependent cellular cytotoxicity or an innate immune response or is

a local, mucosal or systemic immune response and the ISS as a phosphorothioate backbone modification and the ISS has a chimeric backbone. The method further comprises exposing the subject to an antigen, wherein the immune response is an antigen-specific immune response and the antigen is selected from a tumor antigen, viral antigen, bacterial antigen, parasitic antigen and a fungal antigen. The claims is copending Application No. 10/272,502 do not teach a poly T nucleci acid comprising 5'-$X_1X_2TTTTX_3X_4$-3', wherein X_1, X_2, X_3 and X_4 are nucleotides or interspersed poly T motifs or comprising greater than 50% T or at least 24 nucleotides in length or comprises at least 3 T motifs or at least two of the poly T motifs comprise at least three contiguous T nucleotide residues and at least four contiguous T nucleotide residues or is free of two poly A sequences of at least 3 contiguous A nucleotide residues and free of poly-C sequences or is free of methylated CpG dinucleotides or is administered orally or administering a nucleic acid vector encoding an antigen administered separately from the immunostimulatory nucleci acid or administering a peptide antigen. These deficiencies are made up for in the teachings of Krieg et al.

Krieg et al have been described supra.

The claims in the instant application are obvious variants of copending Application no. 10/272,502 because it would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a method of inducing an immune response in a non-rodent subject "comprising" administering a Py-rich or T-rich immunostimulatory nucleic acid species as taught by Krieg et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a method of inducing an immune response in a non-rodent subject "comprising" administering a Py-rich or T-rich immunostimulatory nucleic acid species as taught by Krieg et al because Krieg et al teach a Py-rich nucleic acid which is a T-rich nucleic acid 24 nucleotides in length (see SEQ ID NO:46, Table 12) having the formula 5'-$X_1X_2TTTTX_3X_4$-3', wherein X_1, X_2, X_3 and X_4 are nucleotides and the T-rich nucleic acid comprises a plurality of interspersed poly T motifs and X_1X_2 is TT and X_3X_4 is TT or dinucleotide GT as recited in claim 8 and dinucleotides TG and GT as recited in claim 9 (see SEQ ID NO:53, Table 11). The immunostimulatory nucleic acids taught by Krieg et al are T-rich nucleic acids comprising greater than 50% T and the immunostimulatory nucleic acids are free of two poly A sequences of at least 3 contiguous A nucleotide residues and free of poly-C sequences (see Tables 11-13, SEQ ID NOS:78, 53, 80, 82, 56, 49, 78, 53, 86, 46 and 48). Further, the immunostimulatory nucleic acids taught by Krieg et al are T-rich immunostimulatory nucleic acids comprising at least 3 T motifs (interpreted as single T motifs, see 112, 2nd above) and at least two of the poly T motifs comprise at least three contiguous T nucleotide residues and at least four contiguous T nucleotide residues (see Table 12, SEQ ID NO:46). Krieg et al teach that the immunostimulatory nucleic acid is administered orally (see column 46, lines 55-64). Krieg et al teach that the immunostimulatory nucleic acid can be administered in conjunction with an antigen or a DNA vaccine encoding an antigen, wherein the DNA is separate from the immunostimulatory nucleic acid and the antigen determines the specificity of the

immune response (i.e., is an antigen-specific immune response) (see column 45, lines 36-49).

Claims 1-13, 16-20, 24-25, 30, 34-35, 37-39, 54, 56, 77, 85-87, 94 and 98 directed to an invention not patentably distinct from claims 5, 7-9, 16-18, 20-21, 23-25, 27-30, 34 and 40-41 of commonly assigned Application No. 10/272,502. Specifically, see above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned Application No. 10/272,502, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 35 U.S.C. 103(c) and 37 CFR 1.78(c) to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

17. The examiner notes that certain claims in copending USSNs 10/613,524; 10/644,052 and 10/314,578 and U.S. Patent 6,239,116 B1 are drawn to an invention not patentably distinct from the claims in the instant application and would form the basis of an obviousness-type double patenting rejection, however, in view of the art of Jones et al, Krieg et al and Davis et al above, it is anticipated that Applicant will be amending the claims to narrow the scope of the instant invention. In view of this, Applicant is required to identify those Applications above or otherwise known by Applicant, which are drawn to an invention not patentably distinct from Applicant's newly amended claims in the instant application and file Terminal Disclaimers as appropriate.

Conclusion

18. No claim is allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787. The official fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
571-272-0827